

Examiner reasons that seizures represent a syndrome, rather than a disease and are therefore similar to “pain” which is treatable by aspirin, regardless of the source of the pain.

Applicant respectfully disagrees with the Examiner’s conclusions.

The Examiner’s premise that seizures are a syndrome, not a disease does not accurately reflect the medical community’s approach to treating epilepsy, alcohol withdrawal and other diseases or conditions associated with seizures. Applicant encloses herewith a publication (Feng and Faingold, *Experimental Neurology* (2000) 163:264-270) which demonstrates that seizures associated with alcohol withdrawal and seizures induced in genetically epilepsy prone animals are not both treatable with the same drugs (histamine and adenosine). These authors demonstrate that two drugs, histamine and adenosine, have very different effects on seizures in GEPR-9s [genetically epilepsy prone rats] versus EXT-Rs [ethanol withdrawn rats]. Neither histamine or adenosine showed an effect on seizure intensity or duration in the EXT-Rs, but had an inhibitory effect in the GEPR-9s. The authors conclude that their results “suggests that histamine and adenosine receptors in the IC [inferior colliculus of the brain] of GEPR-9s modulate AGS [audiogenic seizures], but these two agents may be unimportant in modulating AGS in ETX seizures in the AGS initiation site. The reasons for this discrepancy may be due to the chronic nature of AGS susceptibility in GEPR-9s, which contrasts with the acute nature of seizure susceptibility in ETX.” [page 268, col. 2]. These results demonstrate that not all seizures are treatable with the same drugs. Thus, the Examiner’s contention that seizures are merely a syndrome treatable by the same drugs regardless of source is incorrect.

Furthermore, as discussed in Applicant’s response to the final Office Action, the studies reported by Uzbay *et al* are clearly limited to and relevant only to seizures associated with alcohol withdrawal. In particular, this reference teaches that agmatine may be useful in the treatment of

ethanol withdrawal syndrome which includes seizures as a common symptom. The authors concludes that agmatine “has some inhibitory effects on the **withdrawal syndrome** in ethanol-dependent rats.” However, the authors specifically point out that the data concerning the effect of agmatine on the severity and intensity of seizures associated with alcohol withdrawal “did not reach a statistically significant level.”[p. 156, col. 2 and table 2]. Thus, the authors of this work do not conclude or suggest that audiogenic seizures associated with alcohol withdrawal are treatable with agmatine and clearly do not disclose or suggest that seizures in general are treatable with agmatine. The Examiner seems to be confusing the alcohol withdrawal syndrome with seizures associated with alcohol withdrawal. Uzbay *et al* merely conclude that agmatine has an inhibitory effect on **ethanol withdrawal**, but specifically disclaimed any showing of an effect of agmatine on audiogenic seizures associated with alcohol withdrawal, and clearly did not suggest the use of agmatine or its mechanism of action on any other types of seizures.

The results reported in the primary reference actually teach away from the use of agmatine to treat seizures associated with alcohol withdrawal, since it was reported that no statistically significant effects on intensity or duration of seizures were observed. Thus, the skilled practitioner would not conclude that agmatine, which did not have a statistically significant effect on one type of seizure, would have an inhibitory effect on another type of seizure, *i.e.*, epilepsy –associated seizure, particularly since it is known in the art that not all seizures are the same or treatable with the same drugs.

The results reported by Feng and Faingold do not lead to an expectation that the successful use of a particular drug to seizures associated with a particular disease or condition will have an inhibitory effect on seizures associated with another disease or condition, *e.g.*, epilepsy. The results reported by Uzbay *et al.* suggest that agmatine may have no inhibitory effect on seizures associated

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with alcohol withdrawal. For either of these reasons alone, the combined art fails to render the claimed invention obvious.


Accordingly, the rejection of claims 5, 7, 9, 11, and 13-20 under 35 U.S.C. § 103(a) over Uzbay *et al.* and Rajasekaran is traversed and should be withdrawn.

It is respectfully submitted that the present application is in condition for allowance, an early notification thereof being earnestly solicited.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

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